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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,444	01/31/2005	Jean Guy G. Gilles	50304/059001	4465

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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
06/04/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/523,444	GILLES ET AL.	
	Examiner	Art Unit	
	MICHAEL SZPERKA	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,17-22 and 24-36* is/are pending in the application.

4a) Of the above claim(s) *27-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 17-21, 24, 26, and 32-36* is/are rejected.

7)☒ Claim(s) *22 and 25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendments received March 4, 2008 are acknowledged.

Claims 2-16 and 23 have been canceled.
Claims 1, 17, 20, and 22 have been amended.
Claims 32-36 have been added.
Claims 1, 17-22, and 24-36 are pending in the instant application.
Claims 27-31 stand withdrawn from consideration as being drawn to a nonelected invention. See 37 CFR 1.142(b) and MPEP § 821.03, for reasons of record set forth in the restriction requirement mailed May 24, 2007.

Claims 1, 17-22, 24-26, and 32-36 are under examination as they read on anti-idiotypic antibodies, compositions comprising said antibodies, and cells that make said antibodies.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. The rejection of claims 1, 17, 20, and 22 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of applicant's claim amendments received March 4, 2008 which adequately address the issues raised in the rejection of record.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 17-21, 24, and 26 stand rejected and newly presented claims 32-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibodies, cell lines secreting antibodies and compositions comprising antibodies wherein the antibody comprises all six CDR sequences disclosed as SEQ ID NOs:5-10 or wherein the antibody comprises the polypeptides encoded by SEQ ID NOs:1 and 3, does not reasonably provide enablement for antibodies comprising only one recited CDR sequence or random mutations to arrive a recited percent identity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the reasons of record.

The office action mailed September 4, 2007 states:

> Applicants have claimed a genus of antibodies that bind inhibitory antibodies, wherein said inhibitory antibodies bind the C2 domain of FVIII. Inhibitory antibodies that bind FVIII inhibit the ability of FVIII to partake in the coagulation cascade, and as such patients comprising such inhibitory antibodies are prone to excessive bleeding. The specification discloses that BO2C11 is an inhibitory antibody obtained from a hemophilia patient that was used as an antigen to generate an anti-idiotypic response, with the hope that the elicited anti-idiotypic antibodies can be used in therapeutic methods. The idiotype of an antibody is the unique structure formed in an antibody that provides antigen specificity (i.e. CDR loops and nearby framework residues), and it has been observed in the art that antibodies which bind antibody idiotypes often resemble the initial target antigen (i.e. antibody A binds antigen X; anti-idiotypic antibody that binds A comprises an idiotype that structurally mimics the three-dimensional surface of X). Applicants have generated an anti-idiotypic antibody that binds BO2C11 that they have named 14C12, and have indicated that the idiotype of 14C12 mimics FVIII and thus competes with FVIII for binding to inhibitory antibodies. As such, applicants assert that 14C12 can be administered in such a manner such that complexes preferentially form between inhibitor and 14C12, leaving FVIII unbound by inhibitor and thus able to participate in thrombus formation. 14C12 comprises the VH and VL sequences of SEQ ID NOs:2 and 4, which in turn comprise the CDR sequences of SEQ ID NOs:5-10. Therefore it appears that the instant specification discloses a single member of the claimed genus of antibodies, compositions comprising such antibodies, and the cells that make such antibodies. Note that SEQ ID NO:1 encodes SEQ ID NO:2 and that SEQ ID NO:3 encodes SEQ ID NO:4.
>
> It is well established in the art that the formation of an intact antigen-binding site requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three different complementarity determining regions, CDR1, 2 and 3, which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin (Janeway et al., Immunobiology, third edition, 1997, pages 3:7-3:11, see entire selection). It is also known that single amino acid changes in a CDR can abrogate the antigen binding function of an antibody (Rudikoff et al. PNAS USA, 1982, 79:1979-1983, see entire document, particularly the abstract and the middle of the left column of page 1982).
>
> The instant claims recite antibodies comprising sequences at encoded by a polynucleotide at least 95% or 70% identical to either SEQ ID NO:1 or SEQ ID NO:3, as well as antibodies that comprise one or more CDRs that are 95% or 70% identical to SEQ ID NOs:5-10.

Note that the claims reciting CDR sequences do not require all of the recited CDRs to be present in the claimed antibody, nor do they recite where the sequences are located in the antibody. For example, the specification discloses that SEQ ID NO:8 is CDR1 of the heavy chain of 14C12, yet the claims encompass antibodies wherein a sequence of given percent identity to SEQ ID NO:8 is in a different CDR, say CDR3. The claims do not recite, and the specification does not appear to provide guidance, as to which portions of any of the sequences recited by SEQ ID number can be changed and still maintain the capability of binding a human FVIII inhibitory antibody. Note that sequences 95% or 70% identical to SEQ ID NOs:1 or 3 can comprise mutations in the CDR sequences, and the claims reciting CDR sequences explicitly claim antibodies which comprise mutations in the CDR regions. Further, claims 17 and 18 recite that the SEQ ID limitations are applicable to only one chain of the mature antibody such that the sequence of the other chain is not described and thus can literally be anything. Similarly, the antibodies claimed in claim 17 need only comprise a sequence 95% identically to only one of the six CDRs of 14C12, with the other CDRs again being essentially random sequence. Mele et al. disclose an antibody that comprises a sequence 100% identical to SEQ ID NO:9, yet the antibody of Mele et al. binds an antigen unrelated to FVIII inhibitors (of record, see particularly the sequence alignment provided with the restriction requirement mailed May 24, 2007). As such, more structure than what is recited in the instant claims is clearly required to ensure binding to FVIII inhibitory antibodies. Additionally, the specification does not appear to provide guidance as to how much, if any, sequence identity or functional similarity is required of antibodies that are "derived from" 14C12 as is recited in claim 22.

Given the teachings of Janeway et al. that 6 CDR of known binding specificity are required for specific antigen binding and the apparent lack of guidance, direction, or working examples in the specification concerning the pairing and structural location within an antibody molecule of sequences comprising the recited SEQ ID numbers with unknown sequences to generate antibodies comprising the recited functional properties, it does not appear reasonable that antibodies which do not minimally comprise the six CDRs of 14C12, namely SEQ ID NOs:5-10 in their correct spatial relationships would retain the recited functional properties of binding human inhibitory antibodies. Note that SEQ ID NOs:2 and 4 are the complete light and heavy chain variable domains of antibody 14C12 and therefor an antibody comprising both of these sequences would comprise sufficient structure to ensure maintenance of the recited functional properties.

Therefore, based upon the breadth of claimed invention, the lack of clear guidance or working examples as to what changes can or cannot be made to sequences recited by SEQ ID number such that sequences are 70% or 95% identical to said sequences and yet comprise an antibody that retains the recited functional properties, especially given that the claims do not recite where in an antibody these sequences are structurally located, and the art teachings that even a single amino acid change in an antibody can eliminate specific binding to a target antigen, a skilled artisan would be unable to make and use the full scope of applicant's claimed products without conducting undue experimentation.

Applicant's arguments filed March 4, 2008 have been fully considered but they are not persuasive. Applicant argues that the claimed genus of antibodies is enabled because skilled artisans can identify CDR sequences, can make sequences that are a given percent identical to the recited sequences, and can screen for activity as per Example 2 of the instant specification. Applicant further argues that the claimed genus now has recited sequence information for all six CDRs present in the claimed antibodies.

This argument is not persuasive. Independent claim 17 as amended recites "...have at least 95% sequence identity to **one** of the amino acid sequences depicted in SEQ ID NO: ..."(emphasis added by examiner). Thus a reasonable interpretation of the claimed genus is that the claimed antibodies need only comprise sequence identity to two of the recited six CRD sequences, one in the heavy chain and one in the light chain. Thus, sequence/structure information is not provided for all six CDR and thus the independent claims and claims dependent therefrom are not enabled for the reasons of record.

The wording of independent claim 1 is different, reciting "...have at least 70% sequence identity with the **corresponding** amino acid sequences depicted in SEQ ID NO: ..." (emphasis added by examiner). First, the percent identity language allows for sequence variation/mutation in the CDR regions, an unpredictable phenomenon in the absence of additional information concerning conformations and points of contact between the antibody and its cognate antigen as demonstrated by Rudikoff et al. (of record). Further, the CDRs of the claimed antibody are 70% identical to sequences that correspond to the recited SEQ ID numbers. How much identity is there between a recited sequence and a sequence that **corresponds** to the recited sequence? As such, the possible range of mutations and changes to the CDR sequences is much larger than that argued by applicant, and as is discussed in the rejection of record, such mutations are unpredictable.

Note that newly presented claims 32-36 are all dependent claims that do not add additional limitations which obviate the issues of antibody CDR mutations discussed in the rejection of record and thus the new claims are properly joined to the rejection of record.

6. The rejection of claim 25 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for issues surrounding the deposit of named biological materials has been withdrawn in view of the declaration of Jean-Marie Saint-Remy received 3/4/2008 which states that LMBP 5878CB has been deposited in accord with the terms of the Budapest Treaty and states that all conditions as to the public

availability of LMBP 5878CB will irrevocably be removed upon issuance of a patent from this application.

7. Claims 1, 17-21, 24, and 26 stand rejected and newly presented claims 32-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for the reasons of record.

The office action mailed September 4, 2007 states:

> Applicant has broadly claimed a genus of anti-idiotypic antibodies identifiable by their percent identity to either the entirety of the antibody VH or VL domains of antibody 14C12 or by their percent identity to a subsequence of the VH and VL domains, namely the CDRs of 14C12. To support this genus, applicant has disclosed antibody 14C12 which is deposited as LMBP 5878CB. The specification does not appear to disclose what structure within 14C12 is responsible for binding human factor FVIII inhibitory antibodies other than that the CDRs of 14C12 mediate antigen binding. As such, it is not clear what changes can be made to the CDRs of 14C12 such that they maintain a structure that allows for continued antigen binding. Note that the claims explicitly recite antibodies comprising sequence, and therefore structural, alterations, from the sequences disclosed for 14C12. Such claims comprise differences due requirements that the claimed antibodies only comprise one of the recited list of CDRs, as well as the recitation of less than 100% identity for the structural elements that are positively recited.
>
> The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Fri. January 5, 2001, see especially page 1106 column 3).
>
> In University of California v. Eli Lilly and Co. (CAFC) 43 USPQ2d 1398, the court noted: "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene (in the instant case, a peptide) does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes (peptides) may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material."
>
> The court has also noted that "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for

obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

As discussed above, it does not appear that the recited structural features are sufficient to provide a precise definition of an antibody molecule that comprises the recited functional properties, and the disclosure of the single member of the genus, namely 14C12, is not representative of the claimed genus because the important structural elements of 14C12 are not necessarily present in the claimed genus of antibodies.

Therefore, it appears that the broad genus of antibodies claimed by applicants lacks adequate written description because the recited structural requirements, in the instant case amino acids sequences, are not representative of the overall structure of the claimed antibody molecule, nor are the recited structural requirements clearly correlated with the recited functional properties. As such a skilled artisan would reasonably conclude that applicants were not in possession of the claimed genus of antibodies at the time the application was filed. If applicants were not in possession of the claimed genus of antibodies, then it follows that applicants were not in possession of cells that secret the genus of antibodies nor were they in possession of pharmaceutical compositions comprising said genus of antibodies.

Applicant's arguments filed March 4, 2008 have been fully considered but they are not persuasive. Applicant's first argument is that the claims as amended recite antibodies that have 70% or 95% identity all six CDR sequences recited in the instant claims.

This argument is not persuasive because as explained above in conjunction with the enablement rejection, the instant claim language is actually broader than what has been argued by applicant. See above.

Applicant's second argument is that 14C12 is a representative member of the claimed genus and that "Sequence modifications within the 70% sequence identity range are easily recognized and determined or introduced by the skilled person, and its effect on the neutralizing activity of the antibody is determined using methods described in the specification".

This argument is not persuasive because the ability of a skilled artisan to make mutations and screen for activity is pertinent for questions of enablement but is not applicable for written description which is a test of possession. 14C12 is not representative of the entire claimed genus, and therefore does not demonstrate possession of the claimed genus, since while a skilled artisan could identify are recognize sequences which are 70% (or any other arbitrary amount) identical to recited sequences, the same artisan would not, without more, know which of these mutated CDR sequences have the recited functional property of neutralizing FVIII inhibitory

antibodies when present in an antibody molecule. Thus, while the six CDRs of 14C12 have this functional property (i.e. SEQ ID NOs:5-10) the specification does not provide information as to how this structure can be changed such that the recited function is not lost. Thus, it does not appear that the specification discloses an adequate correlation of structure to the recited function of neutralizing to support the breadth of the instant claimed genus of antibodies, compositions of such antibodies, and the cells making such antibodies.

Applicant's third argument is that others using different antigens have succeeded in making antibodies that retain functional activity yet comprise mutations.

This argument is not persuasive since the mutations made for other antibody/ligand pairs are model specific and would not work generically in all antibody/antigen settings, and none of the cited references address the issue of 14C12 antibody binding to FVIII inhibitory antibodies.

Newly presented claims 32-36 are dependent claims and do not add limitations that obviate the grounds of rejection applicable to the independent claims. Thus the newly presented claims are properly joined to the rejection of record.

Claim Objections

8. Claims 22 and 25 are objected to as being dependent upon a rejected independent claim, but would be allowable if rewritten in independent form including all of the limitations of the independent claim and any intervening claims.

9. No claims are allowable.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHAEL SZPERKA whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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